Meeting Minutes from Metoclopramide Meeting at Roberts Laboratories Inc.

Attendees:

Roberts Laboratories Inc:	Dr. M Petrone, Dr. Mohan Kabadi, Dr. Phil Lang, Dr. David Haenick, Mr. Eck Bauer, Mr. Drew Karlans, Ms. Diann Blansett, Mr. Alvin Howard
Ribogene	Dr Anastassios Rezzios
GloboMax LLC	Dr. David Young, Dr. Ruth Oliver, Dr. Sian Bigora, Dr. Gene Heyman and Ms. Patricia Corey-Lyle

Opening of the Meeting:

Dr. Petrone opened the meeting and a general introduction of each attendee was given.

CMC

A milestone has been achieved with regards to formulation development; a nasal spray has been developed which is acceptable to Roberts Laboratories Inc., marketing group.

Issues

The % of and EDTA in the nasal spray is yet to be determined. In the inactive ingredients handbook. the % of allowed is 0.2% per unit volume, and in the FDA approved inactive ingredients guide, the maximum % approved is 0.02%. Presently, it is anticipated that approximately 0.1% per unit volume of is contained in the metoclopramide nasal formulation.

Action items:

1. Calculate % of and if possible EDTA in OTC products in terms of acute and maximum daily dose, per unit dose. Then compare with metoclopramide formulation in terms of acute and maximum daily dose. (Phil Lang,)
2. Check with the poison center at UMAB to see if they can find out the % of menthol and EDTA in other marketed products. (GloboMax,)
3. Determine whether tox formulation can be ready by . (Mohan Kabadi)
4. Clinical Batches should be completed by

TOXICOLOGY

Initiate 1-month primate bridging study to start by (if possible-depends on availability of monkeys). This study should compare the old formulation with the new formulation. In addition, it should be determined how quickly a report for submission to the FDA can be generated. If Roberts are prepared to compensate the toxicological site, a report can be generated within 2 weeks of completion of the study.

REGULATORY

Prepare an IND amendment with regards to the new formulation (CMC) and toxicology studies (3month rabbit and monkey, and the 1-month bridging study). This should be prepared and submitted by (Roberts and GloboMax).

REVIEW OF FDA COMMENTS AND REVISIONS TO CLINICAL PACKAGE

Response to recommendation 1:

"We recommend a placebo arm in phase 1 of the study. In the absence of a meaningful and statistically significant dose response in phase 1, the efficacy of study drug cannot be established and the second phase results may not be adequate to support approval. Analysis of the first study phase results may include treatment failure/withdrawal due to lack of efficacy as an endpoint as well as results of the symptom assessment questionnaire (SAQ). The efficacy results in the second study phase may be enriched by the absence of dropouts from phase one. Efficacy in the phase one intention to treat population is needed to support efficacy in phase two. It may be necessary to drop the placebo arm after phase one. For additional comments on this issue, refer to the Divisions response to clinical question # 3 in the meeting minutes"

A new study design was discussed that would address each of the points presented in the FDA recommendation. A placebo arm will be added to the study and the random withdrawal phase of the study will be dropped. The study will now be placebo-controlled, parallel design comparing both the 10 and 20 mg metoclopramide nasal spray patients to the placebo group. The duration of therapy will be defined as 6 weeks to allow for inclusion of any late "responders". Due to the inclusion of the washout period prior to randomization to the three treatment arms and the inclusion of the placebo group, the averaging of baseline assessments may not be possible.

Response to recommendation 2:

"A global assessment of therapy should be added to support the results of the SAQ."

The recommendation was discussed and a global assessment evaluation will be added to the statistical evaluation.

Action:GloboMax will define a responder by criteria consistent with the efficacy criteria.

Response to recommendation 3:

"Efficacy trends in multiple symptomatic parameters would be important to support any statistically significant result that may depend on single or redundant symptoms. This particularly true if the reflux type symptoms predominate in the differences between groups."

An evaluation of the trends in all symptoms will be conducted. Trends in symptom scores should all be in the same direction. A discussion took place either to:

a) Decrease the number of symptoms in the Perkel scale
b) Change to the Domperidone scale

The consensus of the group was to maintain the Perkel scale in the proposed study with all 9 symptoms being evaluated. However in response to the FDA recommendation the evaluation of the symptoms would be included in the statistical plan. In this plan a trend would be defined as a change in a symptom of greater than or equal to zero. Based on the addition of this evaluation to the statistical plan, it was also decided that the entry criteria based on total symptom score should be redefined.

Action: GloboMax will review the protocol and make a recommendation regarding the new entry criteria.

Response to recommendation 4:

"The proposed scratch-off laminate label containing the identity of the assigned treatment produces a potential for unblinding that may be easily avoided by eliminating this portion of the label"

The recommendation will be accepted and the label modified appropriately.

Response to recommendation 5:

"Protocol deviations/violations and what violations will warrant exclusion from analysis should be stated before beginning the study."

The recommendation will be accepted and a per protocol evaluati n will be included in the statistical analysis plan.

Response to recommendation 6:

"Analysis of dropouts due to lack of efficacy should be included in the efficacy assessment"

The recommendation will be accepted and the protocol modified to include this as a secondary endpoint in the efficacy evaluation.

Response to recommendation 7:

"The definition of the intention to treat populations should be clearly stated"

The recommendation will be accepted and the protocol modified appropriately.

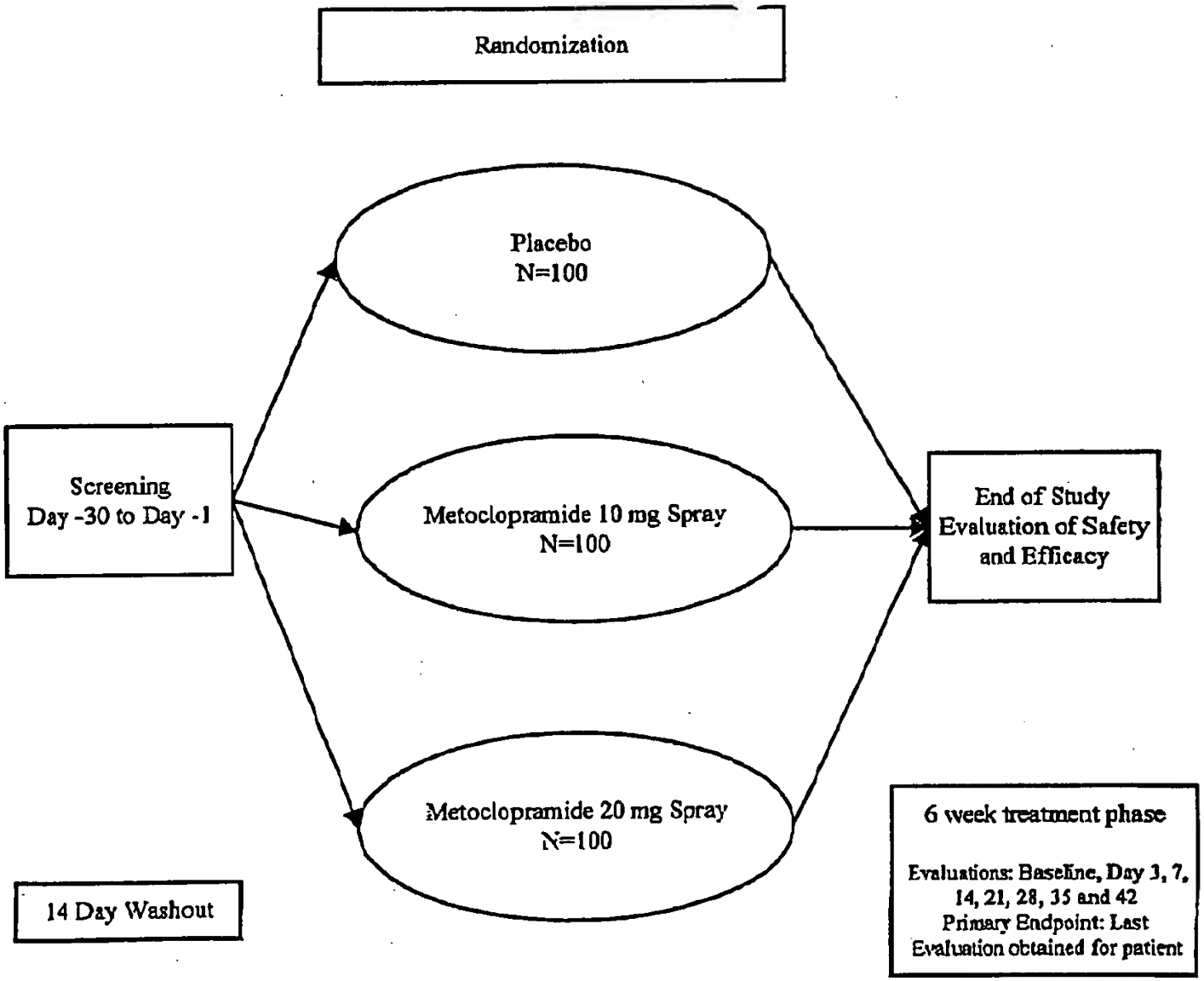

Figure 1. Proposed Study Design for Phase III Study Efficacy Study

Discussion of Phase III Efficacy Design

T pics of discussion related to the study design were:

- Duration of study
- Number of patients in Phase III study
- Number of patients available for inclusion in the ISS

Duration of Study:

The duration of therapy has been changed from 4 weeks in phase I and 4 weeks in phase II of the random withdrawal study, to the 6 weeks in the proposed study. This would allow for late responders to be captured in the efficacy evaluation in this design. The 6-week duration would still allow a clinical response to be detected and would shorten the study. However, the label for the drug would then only be able to indicate therapy for 6 weeks.

Action: Roberts to discuss the ramifications of a 6-week indication versus a 8-week indication with the marketing group at Roberts.

Number of Patients in the Phase III Study:

The proposed number of patients in the study would be 300, 100 mg randomized to each of the three treatment arms. These numbers were based on the ability to detect a difference of 3.5 in the change from baseline mean score with 90% power.
These numbers were acceptable to all parties.

Number of Patients Available for Inclusion in the ISS:

Under current ICH guidelines the requirement for long term safety exposure is "300-600 patients for 6 months". Two issues were discussed in relationship to this guideline.

1. Based on the current Phase II PK/PD study and this proposed study the number of patients to be exposed to the 6 weeks of therapy would be < 200.
2. In the current phase III study, only one 6-week period of therapy is being evaluated. Since the clinical use of this product will be chronic, intermittent use, the FDA may require a longer duration of therapy for safety evaluation. However, the current toxicological program would only provide support for a 3-month study in humans. Additional toxicological study(s) may be required if a longer study, such as 6 month or 1 year was proposed.

Action: GloboMax would develop possible strategies for addressing these issues
by A teleconference would then be scheduled to discuss the strategies.